REMARKS

Reconsideration of this application is respectfully requested.

Status of the Claims

Claims 1-12 were pending in this application. Claims 9 and 10 have been cancelled. Claims 7, 11, and 12 have been withdrawn as being directed to nonelected subject matter. Thus, claims 1-6 and 8 are presented for reconsideration.

Applicant's invention involves a novel use of neurosteroid derivatives, notably pregnenolone, to treat acute or chronic nervous system lesions, in particular certain neurodegenerative diseases, notably linked to the ability of the neurosteroid derivatives to stabilize and/or increase the polymerization of neuronal microtubules.

Studies that demonstrate an effect by pregnenolone (PREG) *in vivo* are very few, but they suggest a beneficial role for this steroid. It was shown that PREG decreased the astrocyte reaction following a cerebral lesion (Garcia-Estrada et al., *Int. J. Devl. Neuroscience* 1999) and in the case of the increased astrocyte size observed during ageing (Legrand and Alonso, *Brain Res.* 1998). It also contributed to improved functional recovery after a medullary trauma (Guth et al., *Proc Natl Acad Sci* USA 1994). PREG protects cells arising from a hippocampal line (HT-22) against toxicity induced by glutamate and the protein beta amyloid (Gursoy et al., *Neurochem Res.* 2001).

PREG is the precursor of all steroid hormones. Their synthesis implies the conversion of the PREG structure Δ5-3β-OH to Δ4-3-keto (implemented by an enzyme called 3β-HSD).

Applicant blocked the Δ5-3β-OH structure of PREG to prevent its metabolism and also to prevent the formation of the ester sulfate of PREG, a molecule that can be neurotoxic at high concentrations. Applicant synthesized a compound, 3-methoxy-pregnenolone (3β-methoxy-pregna-5-ene-20-one, abbreviated as 3-methoxy-PREG), which possesses this property and which, moreover, is at least as active as PREG. The metabolic stability of this compound has been verified by mass spectrometry coupled with gas chromatography. The invention is related to 3-methoxy-PREG, and to all the molecules derived from pregnenolone that contain a 3-methoxy function or present a 3' function that can be converted into 3-methyl ether.

Applicant's molecules are incapable of being converted into metabolites endowed with progestative (progesterone is a direct metabolite of PREG and, in addition to its hormonal activity, it is a PREG antagonist for the polymerization of microtubules), androgenic, estrogenic, and glucocorticoid activity. Also, they cannot be converted into ester sulfates which, like the sulfate of PREG, can have neurotoxic effects.

Applicant discovered that 3-methoxy-PREG, or other molecules according to the invention, play a major role in the polymerization and/or stabilization of microtubules, and present quite remarkable activities for the treatment of pathologies related to the nervous system. Accordingly, this invention provides for the stabilization and/or polymerization of microtubules after administration of the compound of the invention to the host. *See* Specification at page 11, lines 15-18.

In a more general way, the invention relates to increasing the stabilization and/or inducing the polymerization of the microtubules in a cell, comprising the step of exposing the cell to the of 3-methoxy-PREG. Specification at page 12, lies 9-13.

The invention has also as an aim reducing the depolymerization of microtubules and/or the retraction of axons in a cell, comprising the step of exposing the cell to 3-methoxy-PREG. Specification at page 12, lines 26-29.

Claim Rejections - 35 USC § 112 second paragraph

Claims 1-2, 4-6 and 8 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. All dependent claims were included in this rejection. This ground for rejection is respectfully traversed.

According to the Examiner, claim 1 recites a treatment method "comprising the administration to a patient of an effective amount of a drug comprising 3β-methoxy-pregna-5-ene-20-one or a molecule derived from pregnenolone that contains a 3-methoxy function... ", which is indefinite because the general accepted plain meaning of "a drug" is defined as "**a substance**" used as a medicament or in the preparation of medicament, or a substance intended for use as a component of a medicine. It was unclear whether Applicant intended to claim the drug itself administered to a patient or whether Applicant intended to claim the drug, which may also contain an administration vehicle, i.e. carrier, administered to a patient.

This ground for rejection has been obviated by deleting the term “drug” from the claims. Instead, Applicant has used the term “composition,” which contains the 3-

methoxy PREG, and may optionally contain other additives, such as vehicles and/or carriers. Accordingly, Applicant submits that the rejection may be withdrawn.

Claim Rejection - 35 U.S.C. § 102

Claim 9 was rejected under 35 U.S.C. § 102(b) as being anticipated by The Merck Index (Twelfth Edition, 1996: page 1328, compound 7915), as evidenced by Chemical Book (retrieved via www.chemicalbook.com for the structure of pregnenolone methyl ether).

This ground for rejection has been obviated by the cancellation of claim 9. Accordingly, the rejection may be withdrawn.

Claim Rejections - 35 U.S.C. § 103

Claims 1-6, 8, and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Chopp et al. (U. S. Patent No. 6,245,757), as evidenced by Chemical Book (retrieved via www.chemicalbook.com for the structure of pregnenolone methyl ether).

Claims 1-6, 8 and 10 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Stein et al. (U. S. Patent No. 2002/0072509), as evidenced by Chemical Book (retrieved via www.chemicalbook.com for the structure of pregnenolone methyl ether).

Each of these grounds for rejection is respectfully traversed and reconsideration is requested for the following reasons. The rejections will be discussed together since the Chopp and Stein references have the same deficiencies.

According to the Examiner, Chopp et al. teach a method for the treatment of ischemic damage, i.e. damage due to stroke, comprising administering to a mammal afflicted with ischemic cell damage an effective amount of a pharmaceutical composition comprising a progestin and a pharmaceutically acceptable delivery vehicle. The Examiner also contends that Chopp et al. also teach that the method functions by the ability of the progestin to reduce the damage caused by ischemia.

The Examiner contends that Stein et al. teach a method and a composition for the treatment of neurodegeneration following a traumatic injury to the central nervous system by reducing, or eliminating, neuronal cell death, edema, ischemia, and enhancing tissue viability, such that the treatment can enhance survival, proliferation, and/or neurite outgrowth of the neurons that either prevents or retards neuro-degeneration. According to the Examiner, Stein et al. teach that the neuro-protective method is achieved by the administration of a therapeutically effective composition comprising a progestin, or a progestin metabolite, to a patient, i.e. human, wherein the useful progestin, i.e. pregnenolone methyl ether, can be used in the method, as evidenced by Chemical Book for the structure of pregnenolone methyl ether structure (retrieved via www.chemicalbook.com).

Applicant points out that the list of progestins disclosed in Chopp et al. and Stein et al. include not only progesterone or derivatives thereof, but also prior steroid compounds that are turned into progesterone *in vivo*. For instance, the list of progestins disclosed in these documents include pregnenolone (PREG), from which all steroid

hormones are synthesized *in vivo* (see application page 3 lines 22-24 and herein enclosed scheme taken from Wikipedia), including progesterone, the lead progestin.

Applicant demonstrated that 3-methoxy-PREG has the capacity to stabilize or stimulate the polymerization of microtubules *in vitro*. (See Example 2 at page 16 of the specification). However, this effect was not known in the prior art.

Indeed, as mentioned in the application, no significant effect on microtubules can be obtained in vivo using PREG or other derivatives that do not have a blocked Δ5-3β-OH structure, since these compounds are almost immediately converted into other steroid hormones that do not have this property (see application page 3 lines 22-24). For instance, progesterone, one of the main metabolites of PREG *in vivo*, does not have a stabilization or stimulation effect on the polymerization of microtubules (see application, Example 2).

The invention is based on the blocking of the Δ5-3β-OH structure, in order to maintain in vivo the effect of PREG or stabilization or stimulation of the polymerization of microtubules that may otherwise only be observed in vitro (see application page 3 lines 24-33 and page 4 lines 1-12). Although some of the compounds cited in Chopp et al. or Stein et al. may *in vitro* have a stabilization or stimulation effect on the polymerization of microtubules, a significant (and thus therapeutic) corresponding effect cannot be obtained in vivo, since these compounds are almost immediately converted into other steroid hormones that do not have this property.

In summary, Applicant's invention involves the discovery that 3-methoxy-PREG and similar compounds stimulate polymerization and/or stabilization of microtubules

when administered in an effective amount to a subject. While the prior art must provide some foreseeability *In re Kratz*, 201 U.S.P.Q. 71 (C.C.P.A. 1979), this feature was not previously known, and is not described in the Chopp or Stein references. Obviousness cannot be predicated on what is unknown. *In re Rijckaert*, 28 U.S.P.Q. 2d 1955 (Fed. Cir. 1993); *In re Newell*, 13 U.S.P.Q. 1248 (Fed. Cir. 1989). Accordingly, the rejections under § 103(a) should be withdrawn.

Applicant respectfully requests that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 1-8 in condition for allowance. Applicant submits that the proposed amendments of claims 1-8 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner.

Finally, Applicant submits that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account 06-0916.

Respectfully submitted,

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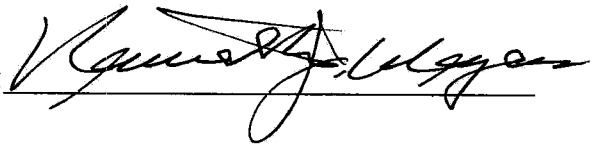
By: 

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